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Dendritic Cell Interactions with NK Cells from Different Tissues

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Conclusion We suggest that this cross-talk should be harnessed by activating both of these innate leucocyte populations with new adjuvant formulations for immunotherapies.

Keywords Myeloid dendritic cells · plasmacytoid dendritic cells · natural killer cell subsets · interleukin-12 · interleukin-15 · type I interferon · DC/NK cell cross-talk

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Introduction

In the immune system, the different leukocytes act not only by mediating their own protective functions, but also by interacting with each other to optimize the response against a pathogen. Recently, relevant liaisons, occurring between natural killer (NK) cells and dendritic cells (DCs), have been extensively investigated, and we will review NK cell activation by DC, editing of DC induced immune responses by NK cells, and an emerging similarity in target cell recognition between these two innate leukocyte subsets. Our discussion will primarily focus on human DC/NK cell interactions.

DCs are critical for initiating immune responses [1]. At an immature stage, they act as sentinels in peripheral tissues, continuously sampling the environment, sensing the presence of pathogens, and secreting chemokines and cytokines to amplify the immune response. Upon activation by danger signals, they up-regulate chemokine receptors and costimulatory molecules, which allow them to migrate into lymph nodes and to efficiently induce T-cell responses [1].

NK cells were identified originally on a functional basis, as this term was assigned to lymphoid cells capable of killing a number of tumor cell lines in the absence of previous stimulation in vivo and in vitro [2]. The molecular mechanisms, by which NK cells discriminate between normal and tumor cells were revealed in recent years. It has been shown that NK cells recognize MHC class I molecules through surface receptors delivering inhibitory signals. As a consequence, NK cells can lyse target cells that have lost (or express low amounts of) MHC class I molecules, a frequent event in tumors or in cells infected by certain cytopathic viruses, primarily herpes viruses. This principle of NK cell activation was coined “missing-self”

recognition [3]. Human NK cells express different HLA class I-specific inhibitory receptors. Those named "killer immunoglobulin (Ig)-like receptors" (KIR) are specific for allelic determinants of HLA class I molecules. In contrast, the Ig-like transcript (ILT)2 (LIR1) receptor is characterized by a broad specificity for various HLA class I molecules, while CD94/NKG2A recognizes the nonclassical MHC class I molecule HLA-E [4–7].

In addition to detection of MHC class I loss, NK cells require also an activating signal for target cell lysis. Absence of activating ligands allows them to spare somatic cells with low MHC class I expression like neurons, and strong activating signaling leads to killing of MHC class I-positive tumor cells. The archetypical activating NK cell receptor is CD16 (FcγRIIIA) [8, 9]. This intermediate affinity Fc receptor allows NK cells to target cells opsonized with antibodies and to mediate antibody-dependent cellular cytotoxicity (ADCC). Triggering receptors specific for HLA class I molecules, displaying a high homology with the corresponding inhibitory receptors, have also been identified on subsets of NK cells [10–12]. However, these receptors cannot account for the NK cell-mediated lysis of HLA class I negative target cells. Indeed, the major receptors responsible for NK cell triggering in the process of natural cytotoxicity are not HLA class I-specific. Three receptors, termed NKp46, NKp30, and NKp44, which are referred to collectively as "natural cytotoxicity receptors" (NCR) were the first activating NK cell receptors to be identified and characterized molecularly [5]. Although a direct correlation has been established between the surface density of NCR on NK cells and the intensity of their cytolytic activity [13], only limited information is available regarding the cell surface ligands recognized by NCRs [14, 15]. An additional activating receptor, NKG2D, is expressed not only by NK cells but also by cytotoxic T lymphocytes. NKG2D recognizes the stress-inducible MIC-A/B [16] and ULBPs proteins [17]. More recently, it has been shown that DNAM-1, a triggering receptor expressed by virtually all NK cells and partially shared with T lymphocytes and monocytes, specifically recognizes PVR (CD155) and Nectin-2 (CD112) [18], two members of the nectin family. Other activating surface molecules include 2B4, NTBA, and NKp80 [5], which contribute to NK cell triggering during the process of natural cytotoxicity. However, it appears that they primarily play a role as coreceptors, i.e., they may amplify the NK cell triggering induced by NCR or NKG2D. Although activating NK cell signals are, therefore, mediated by many receptors, all the available data are compatible with the concept that the ligands for NK cell-activating receptors are mainly expressed by "stressed" cells (e.g., tumor and infected cells or proliferating cells), for which genomic instability might be one hallmark [19].

These NK cell receptors—both inhibitory and activating—allowed for the subdivision of human NK cells and for the analysis of the anatomical distribution of distinct NK cell subsets, which resulted in new insights into NK cell immunobiology.

NK Cell Subsets

For many years, NK cells were considered to be a homogeneous lymphocyte population with excellent cytotoxic capability. Nowadays, NK cells rather appear to comprise various subsets that differ in function, in phenotype, and in anatomical localization.

In human peripheral blood (PB), the majority of NK cells (≥95%) belongs to the $CD56^{dim}CD16^{+}$ cytolytic NK subset [20–22]. These cells carry homing markers for inflamed peripheral sites and perforin to rapidly mediate cytotoxicity. The minor NK cell subset in blood (≤5%) is $CD56^{bright}CD16^{-}$ [20–22]. These NK cells lack perforin (or display low level of it) but secrete large amounts of interferon (IFN)-γ and tumor necrosis factor (TNF)-α upon activation and are superior to $CD56^{dim}$ $CD16^{+}$ NK cells in this latter function [21, 22]. $CD56^{bright}CD16^{-}$ NK cells proliferate more vigorously than their $CD56^{dim}CD16^{+}$ counterparts. Consistent with this feature, they uniquely express the high-affinity receptor for interleukin (IL)-2 (CD25), the alpha chain of IL-7 receptor and CD117, the receptor for the stem cell factor, also named c-kit. In addition, they display homing markers for secondary lymphoid organs, namely, CCR7 and CD62L [20]. Notably, the major histocompatibility complex (MHC) class I allele-specific KIRs are expressed on subsets of $CD56^{dim}CD16^{+}$ cytolytic NK cells, whereas the immunoregulatory $CD56^{bright}CD16^{-}$ NK subset expresses uniformly CD94/NKG2A and lacks KIRs [21]. Therefore, two main functional NK cell subsets have been characterized in peripheral blood, and we will discuss their anatomical distribution next.

NK Cells in Inflamed and Malignant Tissues

During inflammation, activated myeloid DCs (mDCs) and plasmacytoid DCs (pDCs) can secrete different chemokines such as MIP-1β/CCL4, RANTES/CCL5, fractalkine/CX3CL1, IL-8/CXCL8, and IP-10/CXCL10 [23–25]. The different NK cell subsets are able to migrate in response to these chemokines, according to the receptors they express. $CD56^{low}CD16^{+}$ NK cells express CXCR1 and CX3CR1 [20, 26], receptors for IL-8/CXCL8 and fractalkine/CX3CL1, respectively. This last chemokine would mediate the firm adhesion of cells to the endothelium and subsequent migration toward IL-8 [27]. The $CD56^{bright}$ NK cells express CCR5, CXCR3, and CXCR4 which allow

them to migrate in response to RANTES/CCL5, MIP-1β/CCL4, ITAC/CXCL11, and IP-10/CXCL10 [20]. Thus, DCs would attract the two types of NK cells in the site of inflammation, rendering their encounter possible. This hypothetical interaction is supported by in vivo observations, where NK cells have been found in close contact with DCs either in lesions of atopic eczema/dermatitis syndrome or in Gleevec-induced lichenoid dermatitis in gastrointestinal stromal tumor (GIST) bearing patients [28, 29]. However, in autoimmune inflamed lesions primarily the $CD56^{bright}CD16^{-}$ NK cell subset was found to accumulate [30]. While NK cell infiltrates of inflamed tissues have been investigated to some extent, NK cells infiltrating malignant neoplasms have been poorly characterized, although it is clear that NK cells are capable of recognizing and killing tumor cells in vitro. In a recent study, nevertheless, NK cells have been isolated from non-small-cell lung cancers and analyzed in detail [31]. The $CD56^{bright}CD16^{-}$ NK cell subset was consistently observed as being highly enriched in tumor infiltrate and displaying activation markers, including NKp44, CD69, and HLA-DR. Remarkably, lung cancers NK cells were mainly capable of producing cytokines rather than exerting direct cancer cell killing. A similar pattern of NK cell infiltration, characterized by abundant $CD56^{bright}CD16^{-}$ NK cells with low cytolytic activity, has been also reported in renal cell carcinoma [32, 33]. It might be possible that a chemokine environment produced by stromal leukocytes might provide anchorage signals to tumor-infiltrating NK cells. For instance, it has been suggested that heterodimerization of the chemokine receptor CCR5, i.e., the receptor of MIP-1β, leads to an adhesive signal and to the arrest of leukocytes within tissue [34]. Consistent with this notion, only $CD56^{bright}CD16^{-}$ PB NK cells express CCR5 [20], which might explain their accumulation in tumor tissues. Thus both $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{-}$ NK cells might get attracted to inflamed tissues including tumor sites, but only the latter subset might be retained there.

NK Cells in Secondary Lymphoid Tissues

Recent reports have shown that a substantial amount of human NK cells home to secondary lymphoid organs (SLO). These account for around 5% of mononuclear cells in uninflamed lymph nodes (LN) and 0.4–1% in inflamed tonsils and LN [35, 36]. These NK cells constitute a remarkable pool of innate effector cells, since LN harbor 40% of all lymphocytes, whereas peripheral blood contains only 2% of all lymphocytes [37, 38]. Therefore, LN NK cells are under physiological conditions ten times more abundant than blood NK cells. Remarkably, SLOs might not only constitute substantial reservoirs of NK cells, but might even harbor NK cell subsets that are functionally distinct from their peripheral blood counterparts. For instance, $NKp44^{+}$ cells of the mucosal tissue overlaying tonsils and Peyer's patches might primarily secrete IL-22 upon activation [39–43]. This peculiar NK cell receptor carrying cellular subset expresses RORγt and seems to play a pivotal role in maintaining mucosal homeostasis. However, $IL\text{-}22^{+}$ NK-like cells are rare cells with an exclusive localization in the mucosa surrounding the lymphoid follicles, which might be related to the putative protective role of IL-22, triggering bactericidal peptide production against microbial invasion at epithelial and mucosal surfaces. More in general, and as might be anticipated from their CCR7 and CD62L expression, SLO NK cells are mainly composed of the $CD56^{bright}CD16^{-}$ NK cells subset [36]. Like $CD56^{bright}CD16^{-}$ NK cells of peripheral blood, secondary lymphoid tissue NK cells are perforin low/negative and show extremely poor cytolytic activity. Distinguishing $CD56^{bright}CD16^{-}$ SLO NK cells from their PB counterparts, however, is their around fivefold elevated ability to produce IFN-γ in response to activation [44, 45]. In addition, perforin and cytotoxicity can be promptly upregulated on SLO NK cells by cytokines, and at the same time, these cells acquire the expression of CD16, as well as KIRs [36]. Therefore, activation seems to convert secondary lymphoid organ NK cells into cytotoxic effector analogous to blood $CD56^{dim}CD16^{+}$ NK cells. Several studies have indeed recently investigated whether PB-$CD56^{bright}CD16^{-}$ NK cells give rise in vitro and in vivo to cells akin to $CD56^{dim}CD16^{+}$ NK cells and whether SLO can be sites of NK cell maturation [46–48]. These investigations support the hypothesis that $CD56^{dim}CD16^{+}$ develop from $CD56^{bright}CD16^{-}$ NK cells, and that this differentiation can take place both during immune activation in inflamed peripheral tissues, such as reactive LN, and in the steady state. Consistent with this hypothesis, $CD56^{bright}CD16^{-}$ NK cells have longer telomeres than $CD56^{dim}CD16^{+}$ NK cells, and could therefore be their progeny [46, 47]. However, why do NK cells accumulate in SLOs. One possibility is that the resident population of NK cells in lymph node might be derived from blood $CD56^{bright}CD16^{-}$ NK cells, which express CCR7 and CD62L, two molecules involved in lymphocyte trafficking to lymphoid tissues [20]. Alternatively, NK cells might also differentiate directly in SLOs from resident $CD34^{dim}$ $CD45RA^{+}$ hematopoietic progenitor cells [49]. In addition, thymus-derived $CD127^{+}$ mouse NK cells, which show characteristics reminiscent of human $CD56^{bright}CD16^{-}$ NK cells, have been demonstrated to repopulate peripheral lymphoid organs [50]. Finally, long-lived NK cell populations might preferentially home to these sites [51]. Therefore, NK cells harbored in secondary lymphoid tissues could either home there from the blood after their generation in bone marrow or thymus and/or develop there as an independent NK-cell lineage.

NK Cell Activation by DCs

The realization that NK cells are not a homogenous population of innate lymphocytes, but can mount various types of innate immune responses that are either dominated by cytotoxicity or immunoregulatory cytokine secretion, suggests that the repertoire of NK cell responses might be differentially triggered by accessory cells. Dendritic cells (DCs) have been identified as one type of NK cell-activating cells, and preactivation of NK cells by DCs was even found to be required for efficient innate immune responses by these innate lymphocytes against a variety of pathogenic challenges in the mouse [52–54]. Previously, it has been realized that NK cells can be efficiently activated by DCs to elicit antitumor immune responses in mice [55] and to stimulate IFN-γ production, proliferation, and enhanced cytotoxicity of NK cells in humans [56–58]. Of the above-discussed NK cell subsets, the $CD56^{bright}CD16^{-}$ NK cells, which are enriched in secondary lymphoid tissues [35, 36], were found to be especially responsive to activation by DCs [59, 60]. Myeloid DCs preferentially home to secondary lymphoid tissues upon encounter of inflammatory stimuli as well as pathogen constituents and were found to interact with NK cells in perifollicular T cell zones at these sites [59, 61, 62]. However, not only myeloid, but also plasmacytoid DCs can activate NK cells, and these two DC subsets were suggested to stimulate different NK cell functions via distinct signals [63] (Fig. 1). Plasmacytoid DCs have been identified as the main type I IFN-secreting cells upon pathogen encounter [64] and preferentially augment NK cell cytotoxicity via this cytokine [63]. Accordingly, protective NK cell cytotoxicity during infection with the murine cytomegalovirus (MCMV) was found to be type I IFN dependent [65], and these cytokines were preferentially produced by plasmacytoid DCs during this infection [66]. In contrast, myeloid DCs stimulate IFN-γ production by NK cells efficiently via IL-12 and IL-18 [45, 59, 63, 67]. In good agreement, IFN-γ production by NK cells during MCMV infection in vivo was also primarily IL-12 dependent [68]. IL-12 which is essential for resistance to MCMV, comes primarily from myeloid DCs for this innate immune response [66]. Therefore, plasmacytoid and myeloid DCs regulate different aspects of NK cell activation with type I IFN of plasmacytoid DCs increasing NK cell cytotoxicity and IL-12/IL-18 by myeloid DCs primarily triggering cytokine production by NK cells. In contrast to the fairly clear roles of type I IFNs and IL-12 in NK cell activation by DCs, multiple functions have been assigned to IL-15 in this interaction. IL-15 presented on DCs via binding to IL-15Rα has been suggested to stimulate NK cell proliferation [59], survival [69, 70], type I IFN production [71], and priming of protective NK cell responses [52]. These

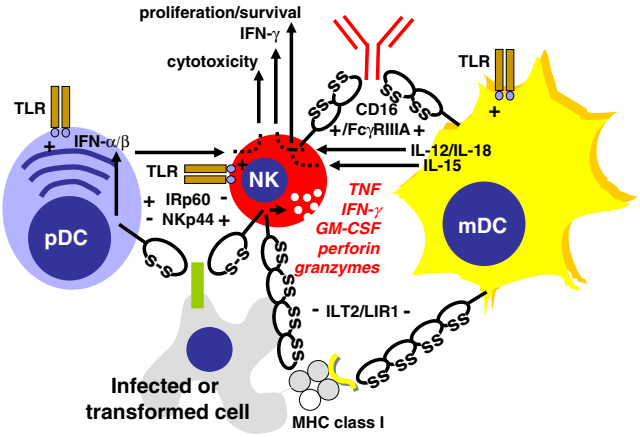

Fig. 1 The cross-talk between dendritic cells (DCs) and NK cells and their shared receptors. Myeloid DCs (mDCs) primarily activate NK cells to secrete cytokines like IFN-γ and to proliferate/survive via production of IL-12/18 and IL-15, respectively. In contrast, NK cell cytotoxicity is primarily triggered via IFN-α/β, which is mainly produced by plasmacytoid DCs (pDCs). NK cells, mDCs and pDCs share pathogen-associated molecular pattern (PAMP) recognition via TLRs. In addition, both NK cells and mDCs get activated upon encounter of antibody opsonized targets via CD16/FcγRIIIA and inhibited via MHC class I recognition by ILT2/LIR1. Contrary to this synchronized activation or inhibition of mDCs and NK cells, pDCs get inhibited to secrete type I IFNs by the activating NK cell receptor NKp44, and vice versa activated to produce IFN-α/β by the inhibitory NK cell receptor IRp60 (CD300a)

functions, in addition to its crucial role during NK cell development [72, 73], identify IL-15 as an essential cytokine for NK cell development and activity, which, depending on the amount produced by DCs under certain stimulation conditions, can probably trigger most NK cell functions. Along these lines, Langerhans cells, a DC subset originally described in skin, was found to produce more IL-15 than other myeloid DC subpopulations, thereby supporting NK cell survival efficiently [74]. Vice versa, maturation with polyinosinic-polycytidylic acid (polyI:C), a toll-like receptor (TLR) 3 agonist, elicited more IL-12 production by myeloid DCs than other maturation stimuli and the resulting DCs stimulated proliferation, cytokine secretion, and enhanced cytotoxicity induction primarily via this cytokine [45]. These studies suggest that NK cells require activation by DCs to reach their full functional potential, and this activation depends on the DC and NK cell subset involved as well as by which stimulus the DCs have been matured.

NK Cell Assistance in T-Cell Priming by DCs

NK cells activated in this fashion can fulfill multiple functions. In addition to the above-discussed mechanisms for infected and transformed target cell recognition, they can also shape consecutive adaptive immune responses by causing

further DC maturation and influencing the polarization of primary T-cell responses. In contrast to editing of immune responses by NK cells that will be discussed in the next section, these functions support protective immune responses against intracellular pathogens and tumors that are most efficiently targeted by Th1 polarized cell-mediated immunity [61, 75, 76]. NK cell assistance in T-cell priming by DCs is best achieved by $CD56^{bright}CD16^{-}$ NK cells [44] and in secondary lymphoid tissues [77], where only low numbers of cytotoxic NK cells are present [58]. NK cell mediate DC differentiation and maturation primarily via TNF and IFN-γ [57, 58, 78]. TNF mainly mediates phenotypical DC maturation with the up-regulation of costimulatory receptors [57, 58], while IFN-γ is required for the differentiation of monocytes into tumor necrosis factor and inducible nitric oxide synthase producing DCs (TipDCs) during granuloma formation like after *Listeria monocytogenes* infection [78]. DC differentiation and maturation allows for the priming of protective adaptive T-cell responses, therefore offering with NK cell recognition and alternative mode of maturation apart from direct recognition of pathogen constituents by DCs [79–81]. Apart from this role in DC differentiation and maturation, IFN-γ produced by NK cells contributes to Th1 polarization by probably also directly acting on T cells during priming [44, 61, 75, 77]. Interestingly, cytokine secreting $CD56^{bright}CD16^{-}$ NK cells are not only enriched in secondary lymphoid tissues, where DC-mediated T-cell priming mainly takes place, but these cells produce also around fivefold more IFN-γ than their peripheral blood counterparts and are, therefore, especially suited to assist in Th1 polarization of primary T-cell responses [44, 45]. These findings document that NK cells are not only activated by DCs, but also influence, in turn, adaptive immune responses that are initiated by these antigen-presenting cells (APCs).

NK Cell Editing of Myeloid APCs

In addition to their support of adaptive immune responses via DC maturation and T-cell polarization, NK cells have also the ability to edit myeloid APCs, including macrophages, DCs, and microglia, in order to possibly avoid immunopathology. This preferentially occurs at high numbers of activated NK cells [58]. Immature DCs can be killed by activated NK cells, and this killing is dependent on the activating NK cell receptors NKp30, NKp46, and DNAM-1 [56, 82, 83]. In contrast, mature DCs are protected from NK cell cytotoxicity via their up-regulation of MHC class I molecules [56]. Especially up-regulation of the nonclassical HLA class I molecule HLA-E and its mouse counterpart Qa1b mediates this protection against mainly CD94/NKG2A carrying NK cells [84, 85]. This cytolytic DC editing by NK cells has been suggested to reduce graft-versus-host disease in bone marrow transplantation [86] and graft rejection in solid organ transplantation [87, 88]. During ameliorated skin graft rejection via this mechanism NK cells homed to lymph nodes and killed there allogeneic DCs in a perforin-dependent manner [88]. Therefore, cytolytic DC editing can limit pathological immune responses. DCs are, however, not the only myeloid APCs that can be edited by activated NK cells. Macrophages can also be targeted by NK cell cytotoxicity. Contrary to DCs, however, they become more susceptible to NK cell lysis by activation with TLR agonists [89–91] or infection [92, 93]. Especially high doses of lipopolysaccharide (LPS), a TLR4 agonist, renders macrophages susceptible to NKG2D-dependent killing by NK cells [89, 90]. Thus, activated, but not resting macrophages are targeted by activated NK cells. A third APC population that can be edited by NK cell cytotoxicity are microglial cells, resident APCs of the central nervous system (CNS) [94, 95]. Similar to DCs, resting microglia is sensitive to NK cell cytotoxicity, whereas activation by TLR4 ligation with LPS protects these cells from NK cell lysis by up-regulation of MHC class I molecules [95]. Resting microglia recognition is mediated by the activating NK cell receptors NKG2D and NKp46 [95]. These studies suggest that resting DCs, activated macrophages, and resting microglial cells can be targeted by activated NK cells, and cytotoxic editing of these myeloid APCs attenuates immunopathology, for example, in transplantation settings.

NK Cell and DC Recognition of Similar Stimuli

Consistent with their concomitant role during the early phase of immune responses, NK cells and DCs are often able to sense similar stimuli in parallel. It has been reported that stimuli acting on TLRs not only activate immature dendritic cells but also render NK cells more prone to receive triggering signals from pathogen-associated molecules, thus exerting a regulatory control on the early steps of innate immune responses against infectious agents [96]. While TLR engagement results similarly for both DCs and NK cells in activation, recognition of self-MHC class I molecules, the main mechanism to restrain NK cell activity, can also inhibit other leukocyte populations. For intance, myelomonocytic cells, including myeloid DCs (mDCs), express ILT2, an inhibitory receptor expressed on subsets of NK cells. This receptor binds MHC class I molecules and delivers a negative signal that inhibits killing by NK cells. In addition, ILT2 engagement also dampens Ca^{2+} mobilization in mDCs triggered through human histocompatibility leukocyte antigens (HLA)-DR [97, 98]. Most recently, plasmacytoid DCs (pDCs), also known as natural interferon-producing cells, have been shown to express receptors that are typically

employed for NK cell recognition. One of these receptor, NKp44, is present on a subset of pDCs in SLOs and is inducible on PB pDCs after in vitro culture with interleukin 3. Crosslinking of NKp44 on NK cells is associated with triggering of NK cell-mediated cytotoxicity. Paradoxically, crosslinking of NKp44 on pDCs does not trigger their functions but significantly inhibits interferon (IFN)-α production in response to cytosine-phosphate-guanosine (CpG) oligonucleotides [99]. Since IFN-α is a potent inducer of NK cell cytotoxicity, the recognition of the same ligand by receptors mediating divergent outcomes might appear contradictory. Nevertheless, pDCs in tonsils are in close contact with $CD8^+$ T cells that are able to produce IL-3 [99]. In this context, expression of NKp44 on pDCs and the inhibition of IFN-α by putative NKp44 ligands would occur when an adaptive response is already taking place, and further, NK cell activation might no longer be required. In addition, IRp60 (CD300a) is another inhibitory receptor expressed by NK cells, as well as by many other leukocytes and also displayed an unpredicted role when cross-linked on pDCs. IRp60 triggering reduced, as expected, TNF-α but increased IFN-α secretion by pDCs [100]. Because exogenous TNF-α, a cytokine abundantly released by activated NK cells, inhibits IFN-α secretion by pDCs [101], these new findings support the notion that there is a balance between IFN-α and TNF-α levels produced by pDC and NK cells. However, pDCs express also CD300c, which shares with CD300a 80% amino acid sequence similarity in their Ig domains. CD300a contains three immunoreceptor tyrosine-based inhibitory motifs (ITIMs), of which at least one is functional in NK cells [102]. CD300c has a short intracellular domain with charged amino acid in the transmembrane domain, which may be associated with other signaling molecules. Thus, although these CD300 receptors may share a common ligand, they almost certainly have different intracellular pDC signaling capabilities. Defining the natural ligands of NKp44 and CD300a/c will shed further light on the complex cross-talk between DCs and NK cells upon recognition of similar stimuli early during immune responses, setting eventually the stage for establishing adaptive immune responses that confer long-term protection.

Conclusions

The cross-talk between NK cells and DCs suggests a critical role for NK cells in the initiation and regulation of immune responses. The considerable knowledge on the molecular basis of these cellular interactions offers opportunities for clinical intervention exploiting DC/NK cell cooperation. Indeed, NK cell activation by DCs is particularly efficient since DC promote both effector functions and survival or proliferation of NK cells. In addition, recent publications in the field of semi-allogeneic bone marrow transplantation have highlighted a beneficial role of NK cells in mediated graft-versus-leukemia effects, and NK cell-based immunotherapies are, therefore, currently being reconsidered [103]. Along these lines, the ability of NK cells to kill tumor cells may facilitate the generation of tumor-derived antigenic material that can be efficiently presented by DCs, further accelerating the induction of tumor-specific immunity [81].

In addition to their traditional role as major innate cytotoxic cells, NK cells have now been shown to regulate immune responses. On one hand, they provide immunoregulatory "helper" functions, being able to activate DCs for pro-inflammatory cytokine production and for efficient Th1 and cytotoxic T lymphocyte (CTL) stimulation. As a matter of fact, DCs activated by NK cells are better inducers of antitumor CTL response, at least in vitro, when compared with the standard mature DCs currently employed in DC-based clinical trials [104]. On the other hand, they can edit myeloid APC populations to attenuate and direct immune responses [105]

All these considerations provide a strong rationale for a combined targeting of NK cells and DCs in novel immunotherapeutic strategies, harnessing this cellular cross-talk in the treatment of patients with cancer and chronic infections that are resistant to conventional therapies.

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